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Concussion in the UK: a contemporary narrative review

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SUMMARY

Concussion has been receiving an increasing amount of media exposure following several high-profile professional sports controversies and multimillion-dollar lawsuits. The potential life-changing sequelae of concussion and the rare, but devastating, second impact syndrome have also gained much attention. Despite this, our knowledge of the pathological processes involved is limited and often extrapolated from research into more severe brain injuries.

As there is no objective diagnostic test for concussion. Relying on history and examination only, the diagnosis of concussion has become the rate-limiting step in widening research into the disease. Clinical study protocols therefore frequently exclude the most vulnerable groups of patients such as those with existing cognitive impairment, concurrent intoxication, mental health issues or learning difficulties.

This up-to-date narrative review aims to summarize our current concussion knowledge and provides an insight into promising avenues for future research.

DEFINITION OF CONCUSSION

Concussion remains a controversial topic to define within the public sphere and medical community alike. In 2017, the international Concussion in Sport Group (CISG) published a definition of *sports-related* concussion (SRC) as a 'traumatic brain injury induced by biomechanical forces', highlighting several common defining features¹:

1. Injury causes an impulsive force to be transmitted to the head.
2. Rapid onset of short-lived neurological impairment that resolves spontaneously.
3. Neuropathological changes may occur, but the acute clinical symptoms largely reflect a functional disturbance that cannot be seen on standard structural neuroimaging.
4. Graded set of clinical symptoms that may involve loss of consciousness (LOC). Resolution typically follows a sequential course but may be prolonged in some cases.
5. The clinical syndrome cannot be explained by drug, alcohol or medication use, other injuries or comorbidities.

Although these criteria are centred specifically toward SRC, the criteria can be applied to all concussion. Confusingly, the term mild traumatic brain injury (mTBI) is often used synonymously with concussion. Currently concussion is equivalent to 'uncomplicated' mTBI where there is no evidence of intracranial injury on CT. 'Complicated' mTBI is

a subcategory of mTBI where intracranial injury is evident on CT scan and all other mTBI criteria are fulfilled.² First defined by the American Congress of Rehabilitation Medicine (ACRM) in 1993 as 'traumatically induced physiological disruption of brain function'.³ The existing ACRM 1993 criteria for mTBI is compared with several potential revisions suggested by a 2021 expert panel survey in [table 1](#).⁴ As highlighted in [table 1](#), expert opinion supports the use of 'mTBI' and 'concussion' synonymously as the recommendations for the ACRM mTBI criteria shift the definition closer toward the CISG concussion criteria.

EPIDEMIOLOGY

mTBI accounts for 1.2% of all emergency department (ED) attenders in England and Wales.⁵ The actual number of patients suffering mTBI however are predicted to be much higher as even where concussions are diagnosed or suspected, studies have demonstrated incorrect hospital coding in 90% of cases making health informatics data unreliable.⁵ Furthermore, the Trauma Audit and Research Network, a prospective, observational registry of patients hospitalized in England and Wales following major trauma, is dominated by those suffering mTBI (68%).⁶ This is despite the registry only including patients with 3 or more days in hospital, admission to intensive or high dependency care, interhospital transfer or death from injury, thereby excluding the majority of mTBI.

Young men and older women are at the highest risk of suffering concussion.^{7,8} In the older mTBI population, the predominant sex is female comprising 64% of those aged over 65 years⁸ but overall, it has a male preponderance.^{7,9,10} Assault, falls and road traffic collisions are the most common mechanisms of injury,^{6,9} with falls accounting for the majority of the very young (<15 years) and older (>65 years) populations.¹¹

Concurrent comorbidities are common. TBI has long been closely associated with acute alcohol intoxication in those presenting to ED with a head injury.¹² Similarly, 30% of all patients with mTBI are reported to have psychiatric illness, and circulatory system illness is in >70% of older patients suffering mTBI.^{13,14}

Multiple psychosocial factors are also linked to a higher prevalence of concussion including, low cognitive function and social deprivation.^{15,16} Of note, 82% of prisoners have reported sustaining a previous TBI and of these 59% give a history consistent with the diagnosis of concussion.¹⁷

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Table 1 Comparison of existing ACRM mTBI definition criteria to suggested revisions by 2021 expert panel

1993 ACRM criteria ³	2021 expert panel suggested revision ⁴
A patient with mTBI is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: 1. any period of LOC; 2. any loss of memory for events immediately before or after the accident; 3. any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented or confused); 4. focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed the following: – LOC of approximately <30 min; – after 30 min, an initial GCS of 13–15; – PTA not greater than 24 hours.	Diagnostic criteria for mTBI should: 1. specify that alternative explanations for altered mental status must be ruled out; 2. incorporate levels of certainty (eg, possible, probable and definite categories) rather than be binary; 3. distinguish between mTBI without; neuroimaging evidence of intracranial trauma; 4. include a maximum timeframe for the onset of symptoms; 5. be expanded to include other observable signs (eg, blank/vacant look or motor incoordination); 6. include a minimum duration of symptoms. Neuroimaging evidence of intracranial trauma implies a more severe form of TBI, not an mTBI. <i>The terms 'concussion' and 'mild traumatic brain injury' can be used synonymously.</i> Rapid-onset postconcussion symptoms after head/neck trauma should indicate at least a possible mTBI.
ACRM, American Congress of Rehabilitation Medicine; GCS, Glasgow Coma Scale; LOC, loss of consciousness; mTBI, mild traumatic brain injury; PTA, post-traumatic amnesia.	

PATHOPHYSIOLOGY

Knowledge of metabolic, structural and inflammatory processes following brain injury is rapidly evolving and the impact on symptomology and long-term sequelae is an expanding area of research. A summary of changes in the neurometabolic cascade, cerebral blood flow, neuroinflammation and cell structure follows.

Neurometabolic cascade

Ionic flux and neurotransmitter release

Shearing and stretching forces initiate intracellular potassium outflow in central neurons and a subsequent diffuse depolarisation.^{18 19} This is known as mechanoporation and causes a widespread depressive depolarisation leading to immediate post-concussion symptoms.²⁰

Compromised gamma-amino-butyric-acid (GABA) interneuron activity allows for exaggerated feedback loops of hyperexcitability and depolarisation due to unregulated glutamate activity.²¹ In animals this is transient and typically normalised within hours.²¹ However, altered glutamate-to-GABA ratios have been seen for days to weeks after concussion in a human sample.²²

Metabolic demand

Increased intracellular sodium and calcium promotes cell damage and mitochondrial impairment,²² leading to a metabolic imbalance. This aggravates the cell damage via excitotoxicity, calcium ion overload, reactive oxygen species, Bcl-2 family, caspases and apoptosis inducing factor.²³ Ineffective metabolism promotes anaerobic energy production and the accumulation of lactate, acidifying the microenvironment.²⁴ This is compounded by compromised cerebral blood flow and feeble oxidative breakdown, meanwhile, glucose hypometabolism renders the brain vulnerable to further damage for an unpredictable length of time.^{20 24–26} Better understanding of the influences on metabolic recovery would help to tailor concussion recovery programs.

Cerebral blood flow and vasculature

Cerebral perfusion

Unlike severe TBI, data for dysregulated cerebral autoregulation in mTBI are reliant on advanced imaging, near-infrared spectroscopy or transcranial Doppler, all of which are almost exclusively research tools.^{27 28} Researchers have postulated that the classic triphasic (hypoperfusion, hyperemia and vasospasm) response seen in severe TBI is mirrored in mTBI,²⁹ and variable regional,

dose and time-dependent changes in cerebral blood flow (CBF) may persist after symptom resolution.^{30 31}

Blood-brain barrier disruption

The blood-brain barrier (BBB) regulates central nervous system (CNS) connections with the periphery through physical barriers, transport, secretions and metabolic blockade.³² In the hours and days following TBI, expression of junctional adhesion proteins decreases leading to greater vessel permeability. The number of endothelial caveolae rise resulting in increased transcytosis of plasma proteins, BBB breakdown and cerebral edema.³³

In animal models a BBB recovery may be 'biphasic', with an early phase disruption, followed by delayed BBB dysfunction days later.³⁴ Neuroimaging has similarly shown BBB disruption that takes days to weeks to recover.^{35 36} MRI studies in humans demonstrated a high prevalence of BBB disruption in athletes with repeated 'subconcussive' head impacts,^{37 38} and BBB permeability has been identified in 73% of patients with a diagnosis of postconcussion syndrome.³⁹ Increased levels of S-100B, a serum biomarker of BBB disruption, show a correlation with poorer neurocognitive and balance scores demonstrating how BBB dysregulation translates to symptomatology.³⁸ While there is sufficient evidence to support BBB dysfunction in TBI, there is a paucity of evidence concerning the magnitude and duration of disturbance following mTBI.

Neuroinflammation

Neuroinflammation in response to concussion has both beneficial and detrimental effects. It occurs via resident glial activation, release of inflammatory cytokines and recruitment of peripheral leukocytes.^{40 41} Microglia produce anti-inflammatory mediators, scavenge cellular debris and choreograph the inflammatory response, yet also produce pro-inflammatory molecules that exacerbate secondary brain injury.⁴² The primary cytokines mediating the inflammatory response following concussion are macrophage inflammatory protein-1 α (CCL3), GRO-KC (CXCL1), interleukin (IL)-1 α , IL-1 β and IL-6.⁴³ When the BBB is interrupted, circulating immune cells and plasma proteins capable of inducing neuroinflammation and cerebral vascular dysfunction (including fibrinogen) are more able to extravasate into the brain.^{44–46}

A prolonged state of neuroinflammation may linger for years and has been hypothesized to correlate with symptom burden and duration.⁴⁷ Prolonged activation of microglia has been

identified up to 17 years following injury and is strongly associated with worsening pathology and outcomes.⁴⁸

Structural changes

Axonal and cytoskeletal injury

Standard neuroimaging cannot detect structural injury following concussion; however, microstructural trauma is thought to play a role in pathophysiology. Diffusion tractography studies have identified multiple areas affected, most frequently the corpus callosum.^{49–51} Many white matter injury measures have been found to correlate with cognitive and neurobehavioral deficits.⁵¹

Neurofilament and microtubule distortion occurs directly from trauma and secondary to high intra-axonal calcium. This disturbs axonal transport and allows the accumulation of beta-amyloid precursor protein leading to axonal swelling.^{52,53} In vitro stretch injury models demonstrated postinjury axonal undulations, beading and plasma membrane permeability.⁵³

Neuronal death

Cell death has recently been seen in mild brain injury animal models,⁵⁴ particularly in the hippocampus and thalamus, causing cognitive deficits.^{55,56} Advanced MRI in humans following a single mTBI has demonstrated diffuse volume loss and atrophy of the limbic system and precuneal cortex.⁵⁷ Although this appears to resolve at 1 year, it is correlated with poorer neuropsychiatric testing performance.⁵⁸

Our current understanding of concussion pathophysiology is limited, however, as we explore the interplay of brain metabolism, neuroimmunology, cerebral physiology and structure changing, we will undoubtedly identify more diagnostic and therapeutic targets.

DIAGNOSIS

No objective test can confirm or disprove a concussive injury. This is a major challenge for diagnosis. In sports, many pitch side tests and metrics aid the gold standard of clinical history and examination, but these are rarely used in non-athlete settings. Advanced imaging, genetic testing and biomarkers are important research tools, but they are yet to prove their utility clinically. There are a vast majority of concussion assessments available⁵⁹; here, the most commonly used concussion tools are discussed.

Clinical

The clinical picture of mTBI can be broadly subdivided into symptoms, physical signs, balance impairment, behavioral changes, cognitive impairment and sleep/wake disturbance¹ as shown in [table 2](#).

Diagnosis is straightforward when individuals fall limp to the ground with LOC following head injury, however, this is complicated when the injury is unwitnessed, insidious, without LOC, symptoms are delayed or there is co-existing cognitive deficit or intoxication. Professional rugby has cameras with replay

capability and thousands of fans and officials, yet concussions are still missed.⁶⁰ The ED is most frequently the only point of contact with medical services for non-athletes suffering mTBI⁷ and current National Institute for Health and Care Excellence (NICE) guidelines focus on triaging serious head injury to relevant neuroscience or neurosurgery centres,⁶¹ but lack any advice on how to diagnose mTBI. Moreover, mTBI investigation is often side-lined when there are distracting injuries. For example, over half of patients with a spinal cord injury have a missed TBI and most of these are concussions.⁶²

One-third of patients with mTBI in ED have concurrent intoxication,⁵ but the CISG definition of concussion states that ‘clinical signs and symptoms cannot be explained by drug, alcohol or medication use’.¹ How then are clinicians to diagnose mTBI satisfactorily in these patients? The CISG also states that ‘clinical signs and symptoms cannot be explained by other injuries (such as cervical injuries, peripheral vestibular dysfunction, etc) or other comorbidities (such as psychological factors or coexisting medical conditions)’,¹ leaving older people and those suffering with cognitive or psychiatric disease more vulnerable to a missed concussion diagnosis.

Imaging

Both the standard MRI brain protocol (T1, T2, diffusion weighted imaging, susceptibility weighted imaging and fluid-attenuated inversion recovery sequences) and CT head show no abnormality in patients with concussion, as per CISG criteria.

Advanced MRI techniques

Diffusion tensor imaging (DTI) is an MRI technique that estimates the white tract anatomy of the brain using anisotropy. DTI shows promise in its diagnostic sensitivity for SRC⁶³ through decreases in fractional anisotropy and increase in mean diffusivity and radial diffusivity.⁶⁴ Magnetic resonance spectroscopy has shown promise as neuronal density and viability, glial density, membrane injury and hypoxia are observable through metabolites. Reduced N-acetyl-aspartate and creatine, and a raised choline are most commonly seen.⁶⁵ Such changes have also been identified in clinical concussion studies but appear independent of symptom burden. However, the ability of functional MRI to detect subtle alterations in CBF in response to stimuli or activities in concussed patients does correlate with severity of postconcussion symptomology.⁶⁶ Similarly, arterial spin labeling (ASL) tends to demonstrate decreased CBF in the brains of concussed patients. This technique is, however, relatively new to the mTBI investigation and methodological variations in the current evidence calls for larger-scale ASL studies.⁶⁷

Advanced MRI techniques are able to detect concussion and monitor recovery in research but are almost never used clinically. They are rarely available and when they are, they are highly time consuming, require specialized radiographers and radiologists

Table 2 Clinical signs and symptoms of concussion

Symptoms	Headache, ‘pressure in the head’, neck pain, nausea or vomiting, dizziness, blurred vision, photophobia, phonophobia, ‘do not feel right’, fatigue, more emotional, irritability, sadness, nervous or anxious, confusion, feeling like ‘in a fog’, feeling ‘slowed down’, difficulty concentrating, difficulty remembering, drowsiness
Physical signs	Loss of consciousness, amnesia, neurological deficit (transient), speech disturbance, lethargy, appears dazed
Balance impairment	Gait unsteadiness
Behavioral changes	Irritability, emotional lability, personality changes
Cognitive impairment	Slowed reaction times, confusion, disorientation
Sleep/Wake disturbance	Somnolence, drowsiness

Table 3 Specific assessments contributing to each domain score of Immediate Post-Concussion Assessment Tool

Verbal memory composite score	Average of these scores: ▶ Word Memory total per cent correct (immediate+delay)/2 ▶ Symbol Match (hidden symbols)/9×100 ▶ Three letters. Total letters correct
Visual memory composite score	Average of the following scores: ▶ X's and O's-total correct (interference) total/4 ▶ Design memory-total per cent correct (immediate+delay)/2
Reaction time composite score	Average of these scores: ▶ X's and O's average correct reaction time (RT) ▶ Symbol Match average correct RT/3 ▶ Colour Match average correct RT
Processing speed composite score	Average of the following scores: ▶ X's and O's-total correct (interference) total/4 ▶ Three letters-average counted correctly×3
Impulse control composite score	Sum of the following scores: ▶ X's and O's-total incorrect–interference ▶ Color match total commissions

and are expensive. Overall, these currently outweigh the benefits they present.

Pitch side tests

The fifth version of the Sports Concussion Assessment Tool (SCAT5) combines symptom, orientation, memory, concentration and balance with clinical neurological examination for assessment of sports mTBI.⁶⁸ Recent investigation into its use in non-athletes showed success in distinguishing concussed from control patients^{69 70} and in Wales, a recent clinical improvement project adapted the SCAT for EDs by removing the sporting reference 'Maddock's questions' and signs at time of injury. The 'ED-CAT' project demonstrated that the SCAT system for public healthcare patients in ED is feasible.⁷¹

Neuropsychological tests

Neuropsychological (NP) assessment is vital in the management of concussion. This is because the time scale for cognitive recovery may not match that of symptom resolution, therefore, a clinical neuropsychologist is needed.⁷² However, when not available, computerized NP assessments, such as the 'Immediate Post-Concussion Assessment Tool (ImPACT)', 'CogSport' or 'Headminer' may be employed. The ImPACT is the most widely used NP assessment and scores verbal memory, visual memory, reaction time, processing speed and impulse control.⁷³ Each composite score is determined through combination of results from a series of cognitive tests (table 3).

The ImPACT scoring requires a pre-injury assessment to which postconcussion scores are compared and a Reliable Change Index is calculated to identify abnormal results.⁷⁴ ImPACT Quick uses percentile scores from large representative samples in place of pre-injury assessment to aid removal-from-play decisions.⁷⁵ Both systems seem promising, however, the need for pre-injury assessment is a clear drawback for use outside of sporting environments. Likewise, ImPACT Quick percentile score calculations exclude individuals with cognitive impairment, learning disability or those over the age of 70 years.⁷⁵ As the majority of those suffering mTBI are older people, this is a clear limitation of the ImPACT in a non-sporting population. In addition, while the ImPACT is available in several non-English languages, not all languages are catered for—an obvious drawback in a multicultural healthcare system.

Biomarkers

Discovery of a diagnostic biomarker is the holy grail of concussion management. A biomarker can be defined as a naturally occurring characteristic that can be objectively measured and interpreted as an indicator of biological processes or responses to therapeutic interventions.⁷⁶ Ideally, a biomarker of concussion should reflect the level of neuronal injury correlating to brain function and outcome in a linear fashion. The only clinically used biomarker for TBI is S-100 β used to determine if a CT scan is warranted for patients following head trauma.⁷⁷ It was incorporated into Scandinavian Neurotrauma Committee TBI guidelines in 2013.⁷⁸ No biomarkers are currently used in the diagnosis or management of concussion.

Traditional serum mTBI markers

S-100 β is a calcium binding protein found in astrocytes that has been shown to be present in TBI, however, it is not brain-specific and can be found in fatty tissue, bone and skin.⁷⁹ There is some evidence to suggest it correlates with increased incidence of postconcussion syndrome (PCS), MRI changes and NP impairment,⁸⁰ but equally strong evidence to disprove this.⁸¹ This variability renders S-100 β of no clinical use in concussion.

Glial fibrillary acidic protein (GFAP) is a filament protein found within the glial cells of the CNS and have been useful in cerebral infarction, preterm neurological abnormalities, encephalopathy and TBI.⁸² Despite evidence that serum GFAP is elevated in TBI, the focus is on CT-positive TBI or neurosurgical cases and is therefore not relevant to concussion.⁸¹

Neuron-specific enolase (NSE) is a glycolytic enzyme found in the cytoplasm of neurons, peripheral neuroendocrine tissue and tumors of the amine uptake and degradation system.⁸³ Evidence for its use in mTBI is often compromised by poor control groups⁸¹ and even in severe brain injury, its long half-life makes distinguishing primary from secondary brain injury a difficulty.⁸⁴ Alpha-II-spectrin is the main structural constituent of the cortical membrane cytoskeleton and levels of spectrin breakdown products (SBDPs) have been reported in CSF from adults with severe TBI, demonstrating correlation with clinical outcome.⁸⁵ When compared with injured-control patients, serum SBDPs have been found to be elevated in patients with concussion⁸⁶ and appear to correlate with MR DTI changes and cognitive impairment at 3 months.⁸⁷

Of all the serum biomarkers, ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) shows the most promise. UCH-L1 is a protein found in the neuronal cell body and in a study of 295 patients, was found to be elevated within the first hour of mTBI and appeared to discriminate concussed patients from control cohort.⁸⁶ Importantly, it appears to distinguish patients with brain injury from those with altered Glasgow Coma Scale secondary to drugs and alcohol.⁸⁶

Salivary microRNA

MicroRNAs (miRNAs) are small non-coding sections of RNA involved in regulating post-transcription gene expression. Concussion-specific circulating serum miR425-5p was first discovered in 2017 to be downregulated in a small sample of athletes concussed within 1 week compared with athletes concussed within 2 weeks and healthy volunteers.⁸⁸ While serum miRNA shows promise for a diagnostic concussion test, it was felt impractical for the purposes of 'pitch side' testing of professional athletes. Saliva has since been suggested as a potential source of miRNA.

Five miRNAs, miR-27b-3p, let-7i-5p, miR-142-3p, miR-107 and miR-135b-5p, have been found to be upregulated in the saliva of concussed players 48–72 hours postinjury compared with matched controls. In addition, this panel of miRNAs showed significant correlation with the reaction time component of the ImPACT assessment.⁸⁹ The most significant results so far came from the Study of Concussion in Rugby Union through MicroRNAs (SCRUM) in 2021 that found a panel of 14 miRNAs that successfully identified concussed rugby players from those with a negative concussion assessment, non-injured controls and musculoskeletal injured controls. The panel was able to differentiate between clinically diagnosed concussion and clinically excluded concussion immediately postmatch and at 36–48 hours. This has significant implications for use in professional sports and for non-athletes in the ED.⁹⁰ Salivary miRNAs are worthy of further investigation in the non-athlete setting where there is a far greater variation in age, physical and cognitive baseline characteristics of patients presenting with head injury.

Tau, neurofilaments, microtubule-associated proteins, cytokines and many more potential biomarkers for mTBI have been researched over the years. In general, study sizes are small, and methodologies are so variable they cannot be compared. There is also wide variation in the results reported. All however agree that a sensitive and specific biomarker for concussion would be a remarkable breakthrough for the management of concussion.

SEQUALAE

Concussion recovery usually occurs within a few days. Occasionally, if symptoms persist beyond 10–14 days, PCS is diagnosed. PCS is complex and historically controversial; however, it is now widely recognized in research and clinical practice as a constellation of non-specific post-traumatic symptoms. These may be linked to other coexisting factors separate from ongoing physiological injury. PCS presents variably and symptoms often fall into the somatic, cognitive, psychological/behavioral and sleep subgroups (table 4).

These symptoms have major impact on quality of life. Eighty-two per cent of patients with mTBI in one large prospective study experienced at least one symptom at 6 and 12 months postinjury.⁹¹ Unfortunately, 40% of the participants demonstrated clinically significant dissatisfaction with life at 12 months using the Satisfaction With Life Score at 12 months postconcussion. Despite media coverage of concussion and PCS in sports, outside of these environments PCS remains problematic to diagnose as symptoms are often non-specific and common to many conditions. Diagnosis also relies on correct original concussion diagnoses which, as previously discussed, is fraught with complication.

MANAGEMENT

As with all other aspects of concussion, the management of sportspeople and non-athletes is astoundingly different. Groups

such as the Rugby Football Union and Football Association implement structured recovery programs focused on rest and graduated return to exercise and contact.^{92–93} The pediatric concussion ethos is to return to education before returning to sport. Yet, in adult non-athlete populations there is almost no structured management of mTBI other than verbal and printed advice that ideally should contain the following⁶¹:

1. Details of the nature and severity of the injury.
2. Risk factors that mean patients need to return to the ED.
3. A specification that a responsible adult should stay with the patient for the first 24 hours after their injury.
4. Details about the recovery process, including the fact that some patients may appear to make a quick recovery but later experience difficulties or complications.
5. Contact details of community and hospital services in case of delayed complications.
6. Information about return to everyday activities, including school, work, sports and driving.
7. Details of support organizations.

There is only vague, unstructured guidance and the quality of discharge advice is entirely dependent on the hospital delivering it. The UK NICE guidance relies on self-diagnosis of PCS and there is no guidance on mTBI service for delegation of care after discharge. A service like this would be logistically challenging and costly but research suggests early intervention can reduce the likelihood of developing PCS in the huge number of individuals suffering mTBI.⁹⁴ Currently, postconcussion follow-up is inconsistent across national healthcare systems with dedicated concussion clinics in some regions and a stark absence of such provision in others.⁹⁵

The ethos of 'return to normal activity' should be applied to all through advice structured around the individuals baseline activity. Advice on sleep, alcohol, driving and time away from work should be implemented alongside targeted medical interventions for early PCS presentation. Programs for returning to premorbid levels of physical activity, or the introduction of physical activity, should be explored from an occupational perspective and as a therapeutic strategy.⁹⁶ Interventions can include pharmacological headache management using non-steroidal anti-inflammatories, beta-blockers, calcium channel blockers, antimigraine medication or peripheral nerve blocks dependent on headache phenotype and associated symptoms.⁹⁷ Adequate NP assessment would help to identify more specific needs for targeted therapies such as treatment of associated affective disorders. In addition, balance and visual assessments may identify the need for focused vestibular, cervical proprioception or oculomotor rehabilitation programs.

THE FUTURE

Great advances in knowledge and clinical application have been made in SRC in recent years. While, no doubt, spurred on by litigation initially,⁹⁸ professional sports are taking steps to protect their players and are actively engaging with mTBI research.⁹⁰ Players are beginning to ask questions about their future brain health and awareness of concussion sequelae among the public has never been so pronounced.

As researchers and clinicians there remain many scientific questions unanswered and large gaps in service provision. Given that almost 80% of those presenting to ED with a concussion never have the diagnosis made,⁵ our epidemiological profile of the disease is likely to be incorrect. This leaves studies open to selection bias and the translatability of any findings inapplicable. The majority of investigatory studies in non-athletes actively

Table 4 Common signs/symptoms of PCS

Somatic	Headache, neck pain, dizziness, poor balance, tinnitus, photophobia, phonophobia, diplopia
Cognitive	Poor short-term memory, difficulties concentrating, slowed reaction times, slower mental processing
Psychological/Behavioral	Irritability, change in personality, fatigue, anxiety, depression
Sleep	Insomnia, hypersomnolence, excessive daytime sleepiness

exclude older people, those with learning disabilities, intoxicated individuals or those with existing neurocognitive issues. As these groups are all at increased risk of head injury, future studies must include such participants if concussion research is to translate into clinical practice.

A specific, objective, diagnostic concussion test would improve detection of mTBI in the ED and give a better reflection of which patients are sustaining this injury. This would improve clinical care for those that were previously undiagnosed and would allow the inclusion of traditionally omitted individuals into concussion studies. A non-invasive, point-of-care test is the ultimate goal and salivary miRNA proves a candidate worthy of investigation in non-sports concussion.

Follow-up of patients following a concussion diagnosis is a huge undertaking. The logistical burden of face-to-face follow-up for all individuals renders an outpatient appointment for everyone non-viable. Innovative approaches to follow-up need to be explored. The COVID-19 pandemic forced healthcare to adapt and adopt more remote methods of patient care. Research into such methods should actively involve patients in the design of the service to maximize engagement and improve accessibility.

Future research should also include management strategies for concussed non-athletes. Existing sports recovery programs have the potential to be tailored for public healthcare patients, but it is unlikely that a 'one-size-fits-all' approach is suitable for non-sportspeople. Strategies for older people, those with additional educational needs and high burden of comorbidity need to be investigated. In addition, the management of PCS symptoms has to extend to these groups also. Medical therapies that are currently used frequently in young sportspeople may be ineffective outside of this cohort and vestibular rehabilitation strategies may need to be modified for the same reason.

For public healthcare funding to be provided for mTBI services, the true monetary cost of concussion to our society must be calculated. The majority of health-economic studies in mTBI have come from the USA and focus mainly on the acute care expense of mTBI.⁹⁹ As discussed, concussion has far-reaching consequences beyond initial management in the ED. Future health-economic studies must extend beyond emergency care to include the cost of PCS. For example, days lost from work, decreased productivity, additional family doctor/ED attendances, treatments for associated vestibular, somatic, mood disorders and so on. To provide a convincing argument to public healthcare funders, a cost saving must be demonstrated and without true baseline cost data this will not be possible.

Concussion can be a devastating disease and although daunting, further research for non-athletes is crucial if we are to identify and support those suffering in our society.

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REFERENCES

- 1 McCrory P, Meeuwisse W, Dvořák J, Aubry M, Bailes J, Broglio S, Cantu RC, Cassidy D, Echemendia RJ, Castellani RJ, et al. Consensus statement on concussion in sport-the 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med* 2017;51:838–47.
- 2 Williams DH, Levin HS, Eisenberg HM. Mild head injury classification. *Neurosurgery* 1990;27:422–8.
- 3 Kay T, Harrington DE, Adams R, Anderson T, Berrol S, Cicerone K, Dahlberg C, Gerber D, Goka R, Harley P. Definition of mild traumatic brain injury. *J Head Trauma Rehabil* 1993;8:86–7.
- 4 Silverberg ND, Iverson GL. ACRM Mild TBI Definition Expert Consensus Group and the ACRM Brain Injury Special Interest Group Mild TBI Task Force. Expert panel survey to update the American Congress of rehabilitation medicine definition of mild traumatic brain injury. *Arch Phys Med Rehabil* 2021;102:76–86.
- 5 Pozzato I, Meares S, Kifley A, Craig A, Gillett M, Vu KV, Liang A, Cameron I, Gopinath B. Challenges in the acute identification of mild traumatic brain injuries: results from an emergency department surveillance study. *BMJ Open* 2020;10:e034494.
- 6 Lawrence T, Helmy A, Bouamra O, Woodford M, Lecky F, Hutchinson PJ. Traumatic brain injury in England and Wales: prospective audit of epidemiology, complications and standardised mortality. *BMJ Open* 2016;6:e012197.
- 7 Brown AM, Twomey DM, Wong Shee A. Evaluating mild traumatic brain injury management at a regional emergency department. *Inj Prev* 2018;24:390–4.
- 8 Albrecht JS, Hirshon JM, McCunn M, Bechtold KT, Rao V, Simoni-Wastila L, Smith GS. Increased rates of mild traumatic brain injury among older adults in US emergency departments, 2009–2010. *J Head Trauma Rehabil* 2016;31:E1–7.
- 9 Sheedy J, Harvey E, Faux S, Geffen G, Shores EA. Emergency department assessment of mild traumatic brain injury and the prediction of postconcussive symptoms: a 3-month prospective study. *J Head Trauma Rehabil* 2009;24:333–43.
- 10 Bloom BM, Kinsella K, Pott J, Patel HC, Harris T, Lecky F, Pearce R. Short-Term neurocognitive and symptomatic outcomes following mild traumatic brain injury: a prospective multi-centre observational cohort study. *Brain Inj* 2017;31:304–11.
- 11 Voss JD, Connolly J, Schwab KA, Scher AI. Update on the epidemiology of Concussion/ Mild traumatic brain injury. *Curr Pain Headache Rep* 2015;19:32.
- 12 Weil ZM, Corrigan JD, Karelina K. Alcohol use disorder and traumatic brain injury. *Alcohol Res* 2018;39:171–80.
- 13 Yue JK, Cnossen MC, Winkler EA, Deng H, Phelps RRL, Coss NA, Sharma S, Robinson CK, Suen CG, Vassar MJ, et al. Pre-injury comorbidities are associated with functional impairment and Post-concussive symptoms at 3- and 6-Months after mild traumatic brain injury: a TRACK-TBI study. *Front Neurol* 2019;10:343.
- 14 Chan V, Mollaveya T, Ottenbacher KJ, Colantonio A. Clinical profile and comorbidity of traumatic brain injury among younger and older men and women: a brief research notes. *BMC Res Notes* 2017;10:371.
- 15 Nordström A, Edin BB, Lindström S, Nordström P. Cognitive function and other risk factors for mild traumatic brain injury in young men: nationwide cohort study. *BMJ* 2013;346:f723.
- 16 Dunn L, Henry J, Beard D. Social deprivation and adult head injury: a national study. *J Neurol Neurosurg Psychiatry* 2003;74:1060–4.
- 17 Schofield PW, Butler TG, Hollis SJ, Smith NE, Lee SJ, Kelso WM. Traumatic brain injury among Australian prisoners: rates, recurrence and sequelae. *Brain Inj* 2006;20:499–506.
- 18 Farkas O, Lifshitz J, Povlishock JT. Mechanoporation induced by diffuse traumatic brain injury: an irreversible or reversible response to injury? *J Neurosci* 2006;26:3130–40.
- 19 Katayama Y, Becker DP, Tamura T, Hovda DA. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J Neurosurg* 1990;73:889–900.
- 20 Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery* 2014;75:S24–33.
- 21 Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train* 2001;36:228–35.
- 22 Yassen AL, Smith J, Christie AD. Glutamate and GABA concentrations following mild traumatic brain injury: a pilot study. *J Neurophysiol* 2018;120:1318–22.
- 23 Cheng G, Kong R-hua, Zhang L-ming, Zhang J-ning. Mitochondria in traumatic brain injury and mitochondrial-targeted multipotential therapeutic strategies. *Br J Pharmacol* 2012;167:699–719.
- 24 Kawamata T, Katayama Y, Hovda DA, Yoshino A, Becker DP. Lactate accumulation following concussive brain injury: the role of ionic fluxes induced by excitatory amino acids. *Brain Res* 1995;674:196–204.
- 25 Kalimo H, Rehncrona S, Söderfeldt B, Olsson Y, Siesjö BK. Brain lactic acidosis and ischemic cell damage: 2. histopathology. *J Cereb Blood Flow Metab* 1981;1:313–27.

- 26 Prins ML, Alexander D, Giza CC, Hovda DA. Repeated mild traumatic brain injury: mechanisms of cerebral vulnerability. *J Neurotrauma* 2013;30:30–8.
- 27 Rangel-Castilla L, Gasco J, Nauta HJW, Okonkwo DO, Robertson CS. Cerebral pressure autoregulation in traumatic brain injury. *Neurosurg Focus* 2008;25:E7.
- 28 Joris PJ, Mensink RP, Adam TC, Liu TT. Cerebral blood flow measurements in adults: a review on the effects of dietary factors and exercise. *Nutrients* 2018;10:530.
- 29 Martin NA, Patwardhan RV, Alexander MJ, Africk CZ, Lee JH, Shalmon E, Hovda DA, Becker DP. Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia, and vasospasm. *J Neurosurg* 1997;87:9–19.
- 30 Wang Y, Nelson LD, LaRoche AA, Pfaller AY, Nencka AS, Koch KM, McCrea MA. Cerebral blood flow alterations in acute sport-related concussion. *J Neurotrauma* 2016;33:1227–36.
- 31 Churchill NW, Hutchison MG, Richards D, Leung G, Graham SJ, Schweizer TA. The first week after concussion: blood flow, brain function and white matter microstructure. *Neuroimage Clin* 2017;14:480–9.
- 32 Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci* 2006;7:41–53.
- 33 Nag S, Manias JL, Stewart DJ. Expression of endothelial phosphorylated caveolin-1 is increased in brain injury. *Neuropathol Appl Neurobiol* 2009;35:417–26.
- 34 Başkaya MK, Rao AM, Doğan A, Donaldson D, Dempsey RJ. The biphasic opening of the blood-brain barrier in the cortex and hippocampus after traumatic brain injury in rats. *Neurosci Lett* 1997;226:33–6.
- 35 Raghupathi R, Conti AC, Graham DI, Krajewski S, Reed JC, Grady MS, Trojanowski JQ, McIntosh TK. Mild traumatic brain injury induces apoptotic cell death in the cortex that is preceded by decreases in cellular Bcl-2 immunoreactivity. *Neuroscience* 2002;110:605–16.
- 36 Shlosberg D, Benifla M, Kaufer D, Friedman A. Blood-Brain barrier breakdown as a therapeutic target in traumatic brain injury. *Nat Rev Neurol* 2010;6:393–403.
- 37 Weissberg I, Veksler R, Kaminsky L, Saar-Ashkenazy R, Milikovsky DZ, Shelef I, Friedman A. Imaging blood-brain barrier dysfunction in football players. *JAMA Neurol* 2014;71:1453–5.
- 38 Marchi N, Bazarian JJ, Puvanna V, Janigro M, Ghosh C, Zhong J, Zhu T, Blackman E, Stewart D, Ellis J, et al. Consequences of repeated blood-brain barrier disruption in football players. *PLoS One* 2013;8:e56805.
- 39 Korn A, Golan H, Melamed I, Pascual-Marqui R, Friedman A. Focal cortical dysfunction and blood-brain barrier disruption in patients with Postconcussion syndrome. *J Clin Neurophysiol* 2005;22:1–9.
- 40 Rathbone ATL, Tharmaradinam S, Jiang S, Rathbone MP, Kumbhare DA. A review of the neuro- and systemic inflammatory responses in post concussion symptoms: Introduction of the "post-inflammatory brain syndrome" PIBS. *Brain Behav Immun* 2015;46:1–16.
- 41 Villapol S, Loane DJ, Burns MP. Sexual dimorphism in the inflammatory response to traumatic brain injury. *Glia* 2017;65:1423–38.
- 42 Loane DJ, Kumar A. Microglia in the TBI brain: the good, the bad, and the dysregulated. *Exp Neurol* 2016;275 Pt 3:316–27.
- 43 Redell JB, Moore AN, Grill RJ, Johnson D, Zhao J, Liu Y, Dash PK. Analysis of functional pathways altered after mild traumatic brain injury. *J Neurotrauma* 2013;30:752–64.
- 44 Das M, Mohapatra S, Mohapatra SS. New perspectives on central and peripheral immune responses to acute traumatic brain injury. *J Neuroinflammation* 2012;9:236.
- 45 Corps KN, Roth TL, McGavern DB. Inflammation and neuroprotection in traumatic brain injury. *JAMA Neurol* 2015;72:355–62.
- 46 Muradashvili N, Lominadze D. Role of fibrinogen in cerebrovascular dysfunction after traumatic brain injury. *Brain Inj* 2013;27:1508–15.
- 47 Blaylock RL, Maroon J. Immunotoxicity as a central mechanism in chronic traumatic encephalopathy-A unifying hypothesis. *Surg Neurol Int* 2011;2:107.
- 48 Ramakrishna AF, Brooks DJ, Greenwood RJ, Bose SK, Turkheimer FE, Kinnunen KM, Gentleman S, Heckemann RA, Gunanayagam K, Gelsos G, et al. Inflammation after trauma: microglial activation and traumatic brain injury. *Ann Neurol* 2011;70:374–83.
- 49 Jang SH, Kim OL, Kim SH, Lee HD. Differences in corpus callosum injury between cerebral concussion and diffuse axonal injury. *Medicine* 2019;98:e17467.
- 50 Ingleson M, Makani S, Johnson G, Cohen BA, Silver JA, Gonen O, Grossman RI. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg* 2005;103:298–303.
- 51 Narayana PA. White matter changes in patients with mild traumatic brain injury: MRI perspective. *Concussion* 2017;2:CNC35–CNC.
- 52 Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. *Exp Neurol* 2013;246:35–43.
- 53 Pettus EH, Christman CW, Giebel ML, Povlishock JT. Traumatically induced altered membrane permeability: its relationship to traumatically induced reactive axonal change. *J Neurotrauma* 1994;11:507–22.
- 54 Prins ML, Hales A, Reger M, Giza CC, Hovda DA. Repeat traumatic brain injury in the juvenile rat is associated with increased axonal injury and cognitive impairments. *Dev Neurosci* 2010;32:510–8.
- 55 Smith DH, Chen XH, Pierce JE, Wolf JA, Trojanowski JQ, Graham DI, McIntosh TK. Progressive atrophy and neuron death for one year following brain trauma in the rat. *J Neurotrauma* 1997;14:715–27.
- 56 Pulella R, Raber J, Pfankuch T, Ferriero DM, Claus CP, Koh S-E, Yamauchi T, Rola R, Fike JR, Noble-Haesslein LJ. Traumatic injury to the immature brain results in progressive neuronal loss, hyperactivity and delayed cognitive impairments. *Dev Neurosci* 2006;28:396–409.
- 57 Zhou Y, Kierans A, Kenul D, Ge Y, Rath J, Reaume J, Grossman RI, Lui YW. Mild traumatic brain injury: longitudinal regional brain volume changes. *Radiology* 2013;267:880–90.
- 58 Zagorchev L, Meyer C, Stehle T, Wenzel F, Young S, Peters J, Weese J, Paulsen K, Garlinghouse M, Ford J, et al. Differences in regional brain volumes two months and one year after mild traumatic brain injury. *J Neurotrauma* 2016;33:29–34.
- 59 Kaufman MW, Su CA, Trivedi NN, Lee MK, Nelson GB, Cupp SA, Voos JE. The current status of concussion assessment scales: a critical analysis review. *JBJS Rev* 2021;9:JBJS.RVW.20.00108.
- 60 Sport BBC. *Saints escape North head injury sanction*, 2021.
- 61 National Clinical Guideline C. *National Institute for health and clinical excellence: guidance. head injury: triage, assessment, investigation and early management of head injury in children, young people and adults*. London: National Institute for Health and Care Excellence (UK) Copyright © National Clinical Guideline Centre, 2014.
- 62 Kushner DS. Strategies to avoid a missed diagnosis of co-occurring concussion in post-acute patients having a spinal cord injury. *Neural Regen Res* 2015;10:859–61.
- 63 Gardner A, Kay-Lambkin F, Stanwell P, Donnelly J, Williams WH, Hiles A, Schofield P, Levi C, Jones DK. A systematic review of diffusion tensor imaging findings in sports-related concussion. *J Neurotrauma* 2012;29:2521–38.
- 64 Khong E, Odenwald N, Hashim E, Cusimano MD. Diffusion tensor imaging findings in Post-Concussion syndrome patients after mild traumatic brain injury: a systematic review. *Front Neurol* 2016;7:156.
- 65 Croall I, Smith FE, Blamire AM. Magnetic resonance spectroscopy for traumatic brain injury. *Top Magn Reson Imaging* 2015;24:267–74.
- 66 Chen J-K, Johnston KM, Collie A, McCrory P, Pizzo A. A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. *J Neurol Neurosurg Psychiatry* 2007;78:1231–8.
- 67 Wang Y, Bartels HM, Nelson LD. A systematic review of ASL perfusion MRI in mild TBI. *Neuropsychol Rev* 2020. [Epub ahead of print: 18 Aug 2020].
- 68 Echemendia RJ, Meeuwisse W, McCrory P, Davis GA, Putukian M, Leddy J, Makdissi M, Sullivan SJ, Broglio SP, Rafferty M, et al. The sport concussion assessment tool 5th edition (SCAT5): background and rationale. *Br J Sports Med* 2017;51:848–50.
- 69 Shapiro JS, Hearn S, Rausa VC, Anderson V, Anderson N, Pugh R, Chau T, Clarke C, Davis GA, Fabiano F, et al. Validation of the SCAT5 and child SCAT5 Word-List memory task. *J Neurotrauma* 2022;39:138–43.
- 70 Luoto TM, Silverberg ND, Kataja A, Brander A, Tenovuo O, Öhman J, Iverson GL. Sport concussion assessment tool 2 in a civilian trauma sample with mild traumatic brain injury. *J Neurotrauma* 2014;31:728–38.
- 71 Mistry DA, Rainer TH. Concussion assessment in the emergency department: a preliminary study for a quality improvement project. *BMJ Open Sport Exerc Med* 2018;4:e000445.
- 72 Bleiberg J, Warden D. Duration of cognitive impairment after sports concussion. *Neurosurgery* 2005;56:E1166.
- 73 ImPact. Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) Normative Data. 2021. http://www.pacificpapermill.com/resources/Concussions/ImPACT_normative_data.pdf.
- 74 Inc IA. *Impact administration and interpretation manual*: ImPACT Applications Inc, 2020.
- 75 ImPact. *Impact quick concussion screening tool for healthcare providers*, 2018.
- 76 . Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001;69:89–95.
- 77 Calcagnile O, Anell A, Undén J. The addition of S100B to guidelines for management of mild head injury is potentially cost saving. *BMC Neurol* 2016;16:200.
- 78 Undén J, Ingebrigtsen T, Romner B. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. *Bmc Med* 2013;11:50.
- 79 Zimmer DB, Cornwall EH, Landar A, Song W. The S100 protein family: history, function, and expression. *Brain Res Bull* 1995;37:417–29.
- 80 Ingebrigtsen T, Waterloo K, Jacobsen EA, Langbakk B, Romner B. Traumatic brain damage in minor head injury: relation of serum S-100 protein measurements to magnetic resonance imaging and neurobehavioral outcome. *Neurosurgery* 1999;45:468–75. discussion 75-6.
- 81 Papa L. Potential blood-based biomarkers for concussion. *Sports Med Arthrosc Rev* 2016;24:108–15.
- 82 Ingebrigtsen T, Romner B. Biochemical serum markers of traumatic brain injury. *J Trauma* 2002;52:798–808.
- 83 Moore BW, McGregor D. Chromatographic and electrophoretic fractionation of soluble proteins of brain and liver. *J Biol Chem* 1965;240:1647–53.
- 84 Toman E, Harrison S, Belli T. Biomarkers in traumatic brain injury: a review. *J R Army Med Corps* 2016;162:103–8.
- 85 Papa L, Robertson CS, Wang KKW, Brophy GM, Hannay HJ, Heaton S, Schmalfuss I, Gabrielli A, Hayes RL, Robicsek SA. Biomarkers improve clinical outcome predictors of mortality following non-penetrating severe traumatic brain injury. *Neurocrit Care* 2015;22:52–64.

- 86 Papa I, Lewis LM, Silvestri S, Falk JL, Giordano P, Brophy GM, Demery JA, Liu MC, Mo J, Akinyi L, *et al.* Serum levels of ubiquitin C-terminal hydrolase distinguish mild traumatic brain injury from trauma controls and are elevated in mild and moderate traumatic brain injury patients with intracranial lesions and neurosurgical intervention. *J Trauma Acute Care Surg* 2012;72:1335–44.
- 87 Siman R, Giovannone N, Hanten G, Wilde EA, McCauley SR, Hunter JV, Li X, Levin HS, Smith DH. Evidence that the blood biomarker SNTF predicts brain imaging changes and persistent cognitive dysfunction in mild TBI patients. *Front Neurol* 2013;4:190.
- 88 SU Z, Di pietro V, Davies D, Wang M, Evans S, Hill L, Grey M, Belli A. Circulating microRNA as novel early biomarker of concussion in elite athletes. *Br J Sports Med* 2017;51:A2.3–3.
- 89 Di Pietro V, Porto E, Ragusa M, Barbagallo C, Davies D, Forcione M, Logan A, Di Pietro C, Purrello M, Grey M, *et al.* Salivary microRNAs: diagnostic markers of mild traumatic brain injury in Contact-Sport. *Front Mol Neurosci* 2018;11:290.
- 90 Di Pietro V, O'Halloran P, Watson CN, Begum G, Acharjee A, Yakoub KM, Bentley C, Davies DJ, Iliceto P, Candilera G, *et al.* Unique diagnostic signatures of concussion in the saliva of male athletes: the study of concussion in rugby Union through microRNAs (SCRUM). *Br J Sports Med* 2021;55:1395–404.
- 91 McMahon P, Hricik A, Yue JK, Puccio AM, Inoue T, Lingsma HF, Beers SR, Gordon WA, Valadka AB, Manley GT, *et al.* Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. *J Neurotrauma* 2014;31:26–33.
- 92 RugbyUnion.org. Application of RFU Concussion Protocols. 2021. <https://www.armyrugbyunion.org.uk/wp-content/uploads/2012/12/Concussion-Headcase-in-the-Army-v5-1.pdf>.
- 93 Association TF. The FA releases new guidelines for managing concussion: @fa. 2021. <http://www.thefa.com/get-involved/fa-concussion-guidelines-if-in-doubt-sit-them-out>.
- 94 Ponsford J, Willmott C, Rothwell A, Cameron P, Kelly A-M, Nelms R, Curran C. Impact of early intervention on outcome following mild head injury in adults. *J Neurol Neurosurg Psychiatry* 2002;73:330–2.
- 95 Mukhtarzada MG, Monteith TS. Equity and disparities in diagnosis, management, and research of post-traumatic headache. *Curr Pain Headache Rep* 2022;26:555–66.
- 96 Schmidt J, Rubino C, Boyd LA, Virji-Babul N. The role of physical activity in recovery from concussion in youth: a neuroscience perspective. *J Neurol Phys Ther* 2018;42:155–62.
- 97 Kamins J. Models for treating post-traumatic headache. *Curr Pain Headache Rep* 2021;25:52.
- 98 Guardian. *Nfl concussion lawsuits explained*, 2013.
- 99 McGregor K, Pentland B. Head injury rehabilitation in the U.K.: an economic perspective. *Soc Sci Med* 1997;45:295–303.